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Formulation, Evaluation And Stability Studies Of Paracetamol IR Tablets

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ABSTRACT

Paracetamol (which is a recommended international non -proprietary name of acetaminophen (acetyl-p-aminophenol, APAP), was synthesized in 1878 by Morse and first introduced into medicine as an antipyretic/analgesic by Von Mering in 1893. Paracetamol (Acetaminophen) is the most commonly used OTC drug. Paracetamol made news headlines early in the pandemic because some governments, including the United Kingdom and France, and the World Health Organization encouraged people with COVID-19 to take Paracetamol rather than ibuprofen – another drug used to help manage symptoms like fever, headache, or body aches. Currently in this pandemic situation COVID-19 the most preferable drug for the COVID patients was the paracetamol during the early stage of affected patients. Paracetamol Immediate Release tablet was prepared by direct compression method by using SSG as a super disintegrant. The prepared tablets were evaluated for Hardness, Weight variation, Friability, Drug content, Dissolution Studies, Stability studies and compared with marketed tablets.

Keywords: Paracetamol, SSG, Dissolution studies, Stability studies, I R tablets.

INTRODUCTION

Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. It is the most popular dosage form and 70% of the total medicinesare dispensed in the form of Tablet. All medicaments are available in the Tablet form except where it is difficult to formulate or administer [1]. Tablets are prepared either by molding or by compression. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive.

Paracetamol made news headlines early in the pandemic because some governments, including the United Kingdom and France, and the World Health Organization encouraged people with COVID-19 to take paracetamol rather than ibuprofen – another drug used to help manage symptoms like fever, headache, or body aches. At the time, there were concernsabout a link between ibuprofen and other drugs that could be

prescribed to COVID-19 patients (such as non-steroidal anti-inflammatory drugs) that could lead to an increased risk for illness or for worsening of COVID-19 symptoms.

While paracetamol is routinely used to relieve COVID-19 symptoms, it is important to strictly respect the dosage prescribed as stated on the medication bottle. The dosage of paracetamol for adults is 2-4 tablets/500 milligrams up to four times in 24 hours, with at least four hours in between doses [2].

Currently in this pandemic situation COVID-19 the most preferable drug for the COVID patients was the paracetamol during the early stage of affected patients.

DIRECT COMPRESSION PROCESS

It is the simplest and most cost-effective tablet manufacturing technique for ODTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tabletting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugar-based excipients.

The manufacture of tablets by direct compression involves comparatively few steps and they include,

1. Premilling of formulation ingredients (active drug substance and excipients).
2. Mixing of active drug substance with the powdered excipients (including the lubricant).
3. Compression of the mixed powders into tablets.

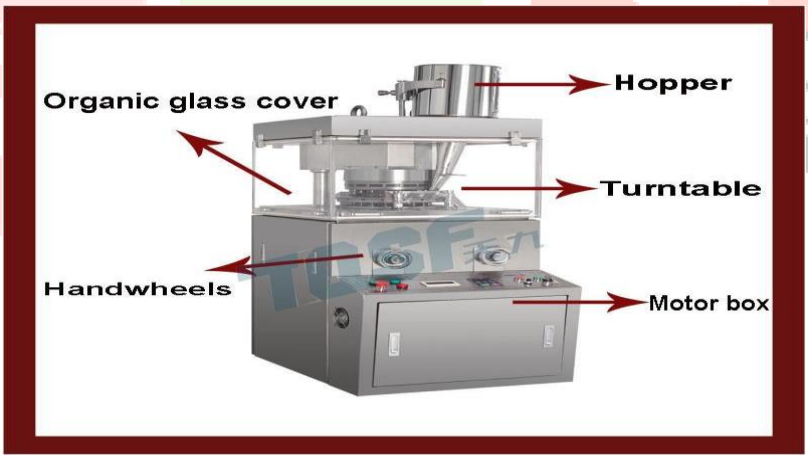


FIG 1 - HIGH SPEED ROTARY TABLET PRESS MACHINE

ADVANTAGES OF DIRECT COMPRESSION TECHNOLOGY

1. Direct compression method requires fewer processing steps (unit operations) and less equipment. Therefore, the method is potentially less expensive than other methods used in tablet manufacture.

2. Tablet manufacture can be carried out without the involvement of moisture and heat. Hence, product stability is almost guaranteed.

3. Some direct compressible excipients possess inherent disintegration properties e.g., Microcrystalline cellulose.

4. Tablets produced by direct compression method generally show faster dissolution times than those prepared by wet granulation.

5. This is because tablets manufactured by direct compression method disintegrate into primary particle state unlike those manufactured by wet granulation method which breaks down into granules and finally into primary particle state.

6. Changes in dissolution profile are less likely to occur in tablets manufactured by direct compression (if stored for a long time) than in those prepared by wet granulation.

7. Because direct compression excipients have a relatively high binding capacity, the pressure required to manufacture the desired hardness is, in general, less with direct compression vehicles than with conventional granulations, resulting in both higher production rates and longer machine life.

8. Lubrication is performed in the same vessel as powder mixing, thereby reducing both transfer losses and contamination of equipment.

STABILITY STUDIES

As per the ICH Guidelines the stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture [3]. Shelf life of the product can be defined as the substance reduces to 90% of its original concentration.

Importance of stability studies

- Product instability of active drug may lead to under medication due to the lowering of the drug in dosage form.
- During the decomposition of the drug or product it may lead to toxic products.
- During the marketing from one place to another during the transportation the drug has the compatibility to change its physical properties.
- Instability may be due to changing in physical appearance through the principles of kinetics are used in

predicting the stability of drug there different between kineticsand stability study [4].

Types of stability studiesPhysical stability

The original physical properties such as appearance, color, dissolution, palatability, suspend ability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

Chemical stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits. This microbiological instability could be hazardous to the sterile drug product [5].

Therapeutic stability

The therapeutic effect (Drug Action) remains unchanged.

Toxicological stability

Toxicological stability has no significant increase in the toxicity occurs [6].

s of stabilitystudies	Storage condition	Minimum time period (Months)
Long term	25±2°C and 60±5% RH	12
Intermediate	30±2°C and 65±5% RH	6
Accelerated	40±2°C and 75±5% RH	6

STABILITY TESTING METHODS

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing.

1. Real-time stability testing:

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time from inter-assay variation. While, testing the samples are collected at regular intervals such that the data is collected at the appropriate frequency such that the analyst can distinguish the degradation day-to-day. The data can be increased by including the single batch of reference material for which stability characteristics have been established. In this the reagents and the instruments used should be in the consistency throughout the stability testing. The control of drift and discontinuity results in the changes of both reagents and instruments should be monitored [7].

Climatic Zones and Long-term stability conditions.

The stability studies are performed worldwide these stability studies cannot be performed at one place as the temperature and other factors vary from country to country and place to place. Due, to this purpose the world has been divided into four zones depending on their climatic conditions so that the degradation of the product and the shelf life could be predicted accurately. Based on this data the real-time stability testing and accelerated stability testing have been derived. [8,9,10,11]

Climatic Zones and Long-term stability conditions

limatic Zones	**Climate**	**Countries**	**MAT***	**ong-Term Testing Conditions**
I	Temperate	United Kingdom, Russia, USA	<15°C/11hPa	21°C/45%RH
II	Subtropical and Mediterranean	Japan, Southern Europe	>15-22°C />11-18hPa	25°C/60%RH
III	Hot and Dry	Iraq, India	>22°C/<15hPa	30°C/35%RH
IV a	Hot and Humid	Iran, Egypt	>22°C/>15-17hPa	30°C/65%RH
IV b	Hot and very humid	Brazil, Singapore	>22°C/>27hPa	30vC/75%RH

MAT*- Mean annual temperature measured in open air

Test Schedule for stability testing of new products

Environment	Sampling Time Points (Months)	Method & Climatic zone
25°C/60% RH	3, 6, 9, 12, 18, 24,36	% RH Long term for zones I and IV
30°C/35% RH	3, 6, 9, 12, 18, 24,36	Long term for zones III
30°C/65% RH	3, 6, 9, 12, 18, 24,36	ong term for zone IV a, or ediate condition forzones I and II
30°C/75% RH	3, 6, 9, 12, 18, 24,36	Long term for zone IV a, or intermediate condition for zones I and II
40°C/75% RH	3, 6, 9, 12, 18, 24,36	Accelerated condition for all zones

METHODS

MARKETED PARACETAMOL TABLETS USED FOR STUDY

Paracetamol tablets of 500 mg strength, of three different brands were purchased from pharmacy Erode, Tamil Nadu, India. The products were coded as A, B, C. All products were manufactured within six months at the time of study. The labeled shelf life of all brands of tablet was 36 months from the date of manufacturing. All brands were evaluated for uniformity of weight, friability, hardness, drug content, disintegration time and dissolution profile as per I.P procedures.

BRAND	COMPANY	DOSAGE FORM	STRENGTH
P-500 (A)	Apex	Uncoated tablet	500mg
Fepanil (B)	Veritaz	Uncoated tablet	500mg
Calpol (C)	GlaxoSmithKline Pharmaceuticals Lt.	Uncoated tablet	500mg

FORMULATION OF PARACETAMOL TABLETS (FD)

S. NO	Ingredients	Quantity (mg)
1	Paracetamol	500
2	Microcrystalline Cellulose	140
3	Sodium starch glycolate	35
4	Magnesium stearate	15
5	Talc	10
6	Total tablet weight	700

Paracatamol tablets were prepared by direct compression method by using Manesty Nova Rotary tablet press. The ingredients paracetamol, cellulose microcrystalline sodium starch glycolate, magnesium stearate and talc were accurately weighed and mixed in geometric proportion. The mixture was sieved in sieve number 100.The resulting mixture was weighed accurately and transferred to 12mm die in a tablet pressand compressed to form the tablets.

CONSTRUCTION OF CALIBERATION CURVE:

Buffer preparation

Phosphate Buffer pH 5.8: Dissolve 27.218 g of potassium di-hydrogen phosphate in a beaker containing 1000ml distilled water. 0.64gm of sodium hydroxide in 80ml distilled water. Mix both the solution and check the pH by using pH meter.

Stock solution

100mg of paracetamol was weighed accurately and then transferred to 100ml volumetric flask. Then add 50ml of 5.8 phosphate buffer stirred and make upto 100ml with sodium hydroxide. From the above solution take 10ml and dilute upto 100ml with water.

From the above dilution take 20ml and dilute upto 100ml with water. Then pipette out 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml, 3ml, 3.5ml, 4ml, 4.5ml and 5ml dilute upto 10ml with water and the solution was measured at 243nm by using UV Spectrophotometer[12].

EVALUATION OF TABLETS

All the branded paracetamol tablets were evaluated for its quality by the followingofficial and unofficial tests. The detailed tests procedures are given below.

1) VISUAL INSPECTION

The shape and color of the different brands of tablets were examined visually and the sizeof tablets was determined using Vernier Caliper.

Shape: roundColor: white
Diameter of the tablet: 12mm

2) WEIGHT VARIATION

20 tablets were selected randomly and weighed individually. The average weight was calculated and individual weight was compared to the average weight. The tablet passes the test if not more than two of the individual weights deviate from the average weight by more than ± 5% and none deviated by twice 5%.

3) HARDNESS TEST

The hardness of the tablets was performed using Monsanto type hardness tester. The hardness of tablets is reported. Standard Value: Tablets should have the Hardness Value between 4 to 6(kg/cm^2).

4) FRIABILITY TEST

This test was performed on 20 tablets using Roche friabilator. The dedusted tablets were weighed and put in the friabilator, after 100 revolutions, the tablets were dedusted and weighed. Percent loss in weight was recorded.

Percentage loss = Initial weight of the tablet-Final weight of the tablet x100

Initial weight of the tablet

5)DISINTEGRATION TEST

Disintegration is the breakdown process of tablets into smaller particles and is the first step towards dissolution. The standard disintegration time for 1.P/USP/BP (Disintegration tester- USP Electro lab: ED-2L). The volume of disintegration medium (900 ml) used was distilled water and the temperature was maintained at 37 ± 2^0C throughout the experiment for each tablet of all the brands. Six tablets of each brand were selected and placed in each of the cylindrical tubes of the basket and the disc was used. The time taken to break each tablet into small particles and pass out through the mesh was recorded. Mean disintegration time was calculated for each of the brands [13]. Uncoated Tablet disintegrates within 15 mins.

6) DISSOLUTION TEST

Dissolution of paracetamol tablet was measured as per IP method, apparatus type 2 paddle used, paddle speed 50rpm per minute in 900ml of pH 5.8 phosphate buffer (Potassium di-hydrogen ortho phosphate) solution at $37\pm2\ ^0$C. Check the absorbance of paracetamol tablet by using UV visible spectrophotometer.

Each sample was spectrophotometerically determined at 243nm wavelength.

1ml of the sample was taken at different time intervals. 1ml sample was withdrawn and replaced with dissolution medium. 1ml of the sample solution was filtered and further diluted to 10ml with phosphate buffer. The process was repeated for all the four batches [14].

7)DRUG CONTENT

Weigh and powder 20 tablets. Weigh a quantity of the powder containing about 0.15g of paracetamol, add 50 ml of 0.1M sodium hydroxide, dilute with 100 ml of water, shake for 50min and add sufficient water to produce 200 ml. Mix, filter and dilute 10.0 ml of the filtrateto 100ml with water. To 10ml of the resulting solution add 10ml of 0.1M sodium hydroxide, dilute to 100 ml with water and mix. Measure the absorbance of the resulting solution at the maximum at about 257nm. Calculate the content of $C_8H_9NO_2$ taking 715 as the specific absorbance at 257nm.

STABILITY STUDIES

STABILITY STUDY PROTOCOL

The stability testing is one of the processes for drug development. Stability data for the stability studies are used to determine the storage conditions and packaging materials for a bulk of the prepared formulated products. The stability studies are used to determine the expiry date of the substance. These stability protocols are pre-requisite for the stability studies and necessary a written document that has a key of instructions for the regulation and well- controlled stability studies. Each formulation has different types of containers to be packed hence the protocol can also depend on the type of the drug substance. The protocols can also depend on the drugs already in the market and the newly prepared drugs. The protocols should reflect the regions that are proposed by the ICH. A well-designed stability study protocol should include the following information:

1. Number of batches.
2. Containers and Closures.
3. Orientation of storage of containers.
4. Sampling time points.
5. Test storage conditions.
6. Test parameter

1. Number of batches

Stability testing is carried out in batches as performing the stability study in a single step is difficult hence, they are divided into batches. For a product that is stable without any reactions the stability studies are performed on a single batch. When the substances are unstable or not when the drug is newly registered the stability studies are performed on three batches. When any one of the batches shows unstable activity then the stability is performed for six respective batches if the unstable repeats, then the whole product formulated must be discarded as they cannot be administered. The initial data is not a full-scale production batch, the first three batches should be post approval which are long term studies using the same protocol as in approved drug applications. The data collected from the laboratory are not accepted for the primary stability data. The selections of batches contribute to the random sample from the population of pilot or production batches.

2. Containers and Closures

The selection of containers and closures is very important and stability studies on containers and closures as when the products are to be packed in the suitable medium. The packaging materials include the aluminum strip packs, blister packs, Alu-Alu packs, HDFE bottles etc., this may also include the secondary packaging but not the shippers. The products packed in all closures are to be tested for the stability studies as the unsuitable container can degrade the drug physically. For, the bulk containers the prototype containers are allowed. While packaging is done the prepared drug is placed in the suitable containers as the containers can contaminate the product and shelf life of the drug can be reduced than theactual time.

3. Orientation of storage of containers

The samples of solutions, semi-solid drug products for stability studies must be placed upright in such a way that the drug encounters the containers. This helps to know that when the drug encounters the containers is undergoing any chemical changing which leads to the degradation of the drug. This degradation may be due to the absorption or loss of water.

4. Sampling time points

The testing is important at time intervals to establish the stability profile of the new drug substance. The products with a shelf life of months in the first year, then 6 months for the second year and then yearly thereafter throughout the prediction of shelf-life. In the case of accelerated stability studies, a minimum of three time points like 0, 3, and 6 months. In case, when the same product of different strength, size etc to be tested. Retained stability testing can be used which involves a smaller number of points. The reduced testing plans are based on the bracketing and matrixing statistical designs. Bracketing is the design only when the samples on the certain design factors such as strength and package size are tested at all the three time points as in full design. The factors that can be matrixes can include the strength, batches, container sizes, and intermediate time points [9,15].

5. Test storage conditions

The storage conditions to be selected based on the climatic zones in which the product must be marketed. General recommendation on the storage conditions has been given by ICH,CPMP, and WHO.

6. Test parameters

The test parameters used in the stability studies must be evaluated of the stability samples. The test of sample mainly includes the quality, purity, efficacy, and identity which can be depending upon the climatic conditions. Therefore appearance, assay, degradation products, microbiological tests include sterility, preservative measures etc. The stability testing batches should also reach the testing parameters including the heavy metals, residue of ignition, residual solvents, etc. These tests have also been discussed in the ICH guidelines (QA6).

Stability Studies Equipment

The equipment used for stability testing is called stability chamber. These are specialized environmental chambers that can simulate the storage condition and enable evaluation of product stability based on real-time, accelerated, and long-term protocols. They are available in both walk-in and reach-in styles. Smaller chambers are preferred for accelerated testing, as the retention time of products is much less in these cabinets, while the walk-in chambers are preferred for long-term testing. Such chambers or rooms are engineered and qualified to ensure uniform exposure of the set conditions to all the samples in the chamber. These chambers are expected to be dependable and rugged because of the requirement of uninterrupted use for up to years. They are fitted with appropriate recording, safety, and alarm devices. In addition, photo stability chambers are also available and utilized both with and without temperature and humidity control. Two types of light sources are usually employed in photo stability chambers, one is the combination of cool white & near UV fluorescent tubes and second one is artificial day light lamps e.g.: xenon or metal halide. It is required to obtain a total exposure of 1.2 million lux hour. The visible light intensity is estimated using a lux meter. The calculation is made on how many hours of exposure are needed [9,16].

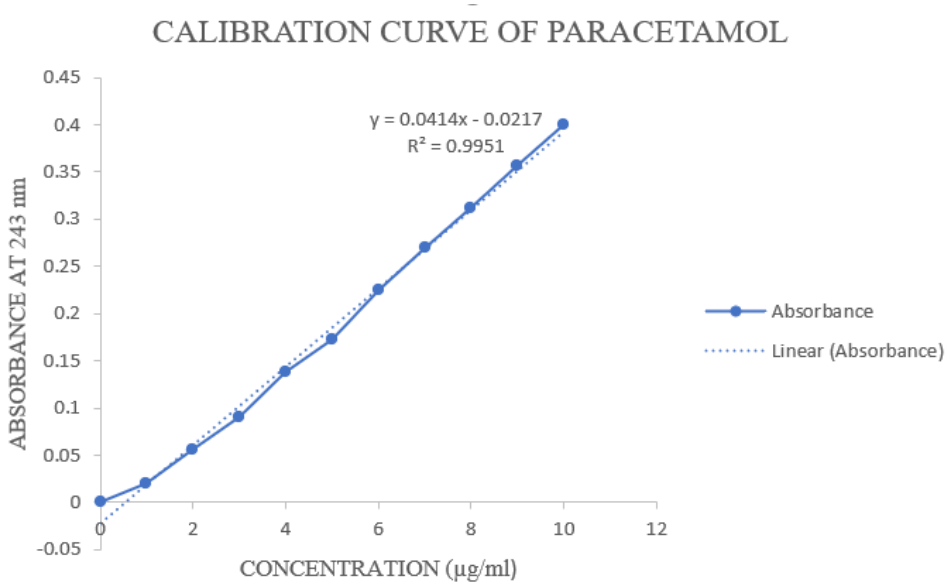
Evaluation of stability studies

A systematic approach must be done in evaluating the stability studies which may include results from the physical, chemical, biological, and microbiological tests, even including the dosage forms of the substances. These evaluations help to know the degradation of the product with the analysis of the data obtained during testing. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine all the data into one to estimate. When the substance starts showing the degradation and with the data analysed the shell life is apparently predicted.

RESULT AND DISCUSSION

CONSTRUCTION OF CALIBRATION CURVE OF PARACETAMOL

Concentration µg/ml	Absorbance at 243nm
0	0.000
1	0.02
2	0.056
3	0.091
4	0.138
5	0.172
6	0.225
7	0.27
8	0.312
9	0.356
10	0.4



EVALUATION TEST FOR TABLETS

Weight Variation Test (gm)

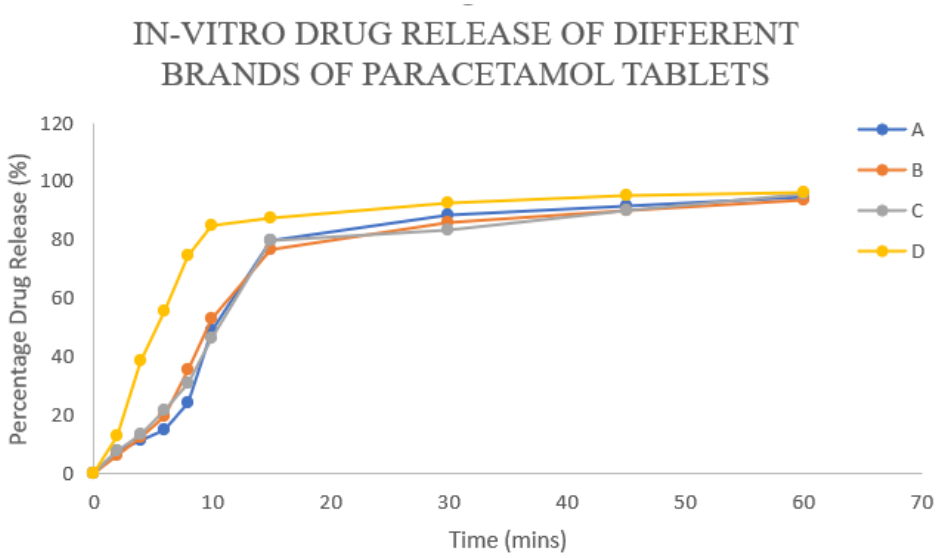
S.NO	P-500	Fepanil	Calpol	Formulation
	A	B	C	D
1	0.590	0.560	0.620	0.700
2	0.590	0.560	0.620	0.690
3	0.580	0.560	0.620	0.700
4	0.590	0.540	0.620	0.680
5	0.590	0.560	0.620	0.700
6	0.600	0.560	0.620	0.690
7	0.590	0.560	0.630	0.700
8	0.590	0.540	0.620	0.700
9	0.590	0.560	0.620	0.690
10	0.590	0.560	0.620	0.680
11	0.590	0.560	0.640	0.690
12	0.590	0.560	0.620	0.700
13	0.590	0.560	0.620	0.680
14	0.590	0.560	0.620	0.680
15	0.590	0.560	0.620	0.690
16	0.590	0.560	0.620	0.700
17	0.590	0.560	0.620	0.690
18	0.590	0.560	0.620	0.700
19	0.590	0.560	0.620	0.680
20	0.590	0.560	0.620	0.690
Total weight	11.8	11.16	12.43	13.83
Average	0.590	0.558	0.621	0.691

Hardness test, Friability test, Disintegration test & Drug content

S. No	SAMPLE	Codes	Hardness Test (kg/cm^2)	Percentage friability (%)	Disintegration Time (mins)	Percentage Drug content (%)
1	P-500	A	4.03	0.84	3.00	98.2
2	Fepanil	B	3.86	1.00	2.40	99.57
3	Calpol	C	3.75	0.321	3.20	99.29
4	Formulation	D	3.68	0.95	30 sec	98.45

Comparative *In –vitro* Dissolution studies (A-B-C-FD)

Time (mins)	P-500	Fepanil	Calpol	Formulation
	A	B	C	FD
0	0.00	0.00	0.00	0.00
2	7.71	6.43	8.14	12.85
4	11.57	12.42	13.71	38.57
6	15.00	19.71	21.85	55.71
8	24.42	35.57	30.85	74.99
10	49.28	53.14	46.28	85.00
15	80.00	76.71	79.71	87.42
30	88.70	86.14	83.57	93.00
45	91.7	89.96	90.42	95.56
60	94.71	93.85	95.99	96.43



STABILITY STUDY RESULTS

Stability Chamber	Temperature	Humidity
S1	30ºC	65%RH
S2	35ºC	70%RH
S3	45ºC	75% RH

STABILITY RESULTS OF FORMULATED TABLET (FD)

Evaluations made	At initial (0 month)			At the end of 3 months			At the end of 6 months		
	S1	S2	S3	S1	S2	S3	S1	S2	S3
Percentage Drug Content (%)	98.45	98.45	98.45	97.2	96.49	94.78	96.54	95.69	93.23
In-vitro dissolution study	96.43	96.43	96.43	95.13	94.28	93.85	94.27	93.71	92.57

CONCLUSION

The present study was concluded that to develop and formulate immediate release tablets of Paracetamol with Sodium starch glycolate as a super disintegrant and microcrystalline cellulose used as directly compressible excipients. The post compression parameters like hardness, friability, disintegration time and In-vitro drug dissolution studies were carried out and compared with marketed tablets and the values were found to be within limits. Based on the ICH Guidelines the stability study of the formulated tablets (FD) were carried out in the stability chamber S1, S2 & S3 showed the percentage of drug release 94.27%, 93.71% & 92.57% respectively at the end of 6 months, these results indicates that no significant changes in the formulation.

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